REMARKS

I. Claim Status. Claims 1-8 and 11-20 are under examination. Claims 1, 4, 8 and 13 have been amended, without prejudice or disclaimer. Support for the amended claims is found throughout the specification, e.g., at pages 5-11 and 20 (for claims 1, 8 and 13) and at pages 9-10 (for claim 4). Each amendment to the claims is supported by the application as filed. Accordingly, by this Amendment, no new matter has been added to the application.

II. Amendment to the Specification. The specification has been amended to correct an obvious editorial error, by replacing the term --thrombinase-- with "thrombin." The editorial nature of the amendment is self-evident from the context of the sentence in which the term appears. One of ordinary skill in the art would find it self evident that "thrombin [not thrombinase] is produced as a result of the prothrombinase catalysis of prothrombin." *See also* specification at page 6, lines 17-18. ("Prothrombinase refers to any substance which cleaves prothrombin in a manner which converts the prothrombin to thrombin.") Thus, the amendment to the specification does not add new matter to the application.

III. Objection to the Specification. The Examiner has objected to the specification as being unclear. In response, the specification has been amended as set forth above in Part II. The basis of the rejection is believed to have been addressed. The objection should be withdrawn.

IV. Claim Rejections. The rejections set forth in the Office Action are summarized and addressed below.

(i) Rejections Under 35 U.S.C. § 112, second paragraph. Claims 1-8, and 11-20 have been rejected as allegedly being indefinite.

(a) Claims 1 and 13. The Examiner asserts that in claims 1 and 13 the recitation of "the property" lacks antecedent basis and is indefinite since it is unclear what physical structures or procedural steps are required for "said product" or "said substrate" to have "the property." In response, without conceding the validity of the Examiner's position, claims 1 and 13 have been amended. It is clear that "a property" refers to the requirement that the product "does not activate platelets." Thus, the rejection is believed to have been addressed and overcome.

Additionally, the Examiner contends that the preamble in claim 1 does not correspond to the method outcome, since it is not clear how "assaying a [thrombin] product" amounts to an assay for the "activation state of platelets." In response, without conceding the validity of the rejections or the Examiner's position, claim 1 has been amended to recite a method that comprises "reacting a mixture comprising platelets, a prothrombin-converting enzyme, and a substrate of the prothrombin-converting enzyme to produce a product, and assaying the product produced in step (a), said product having a property that said product does not activate platelets, and thereby assaying the activation state of said platelets." *See* amended claim 1.

Claim 1 recites a quantitative assay for the activation state of platelets. As set forth in the specification, only activated platelets will provide the factors required for prothrombinase (i.e., a prothrombin-converting enzyme) activity. Hence, the amount of substrate converted to product in step (a) of claim 1 will depend directly on the activation state of the platelets present in the mixture called for in claim 1, step (a). Step (b) merely assays the product formed in step (a). Accordingly, one of ordinary skill in the art would readily recognize that the steps called for in claim 1 measure the activation state of the provided platelets.

In short, "assaying a [thrombin] product" amounts to an assay for the "activation state of platelets" because only activated platelets will provide the factors required for active prothrombinase; thus only the presence of activated platelets in step (a) would lead to production of a thrombin product. Claim 1 recites all the steps required for a "method for assaying activation state of platelets." Accordingly, the present rejection should be withdrawn.

(b) Claim 4. The Examiner contends that the recitation of "exogenous" in claim 4 is indefinite since the point of reference defining the boundary between "exogenous" and "not exogenous" is not clear. In response, and without conceding the validity of the rejections or the Examiner's position, claim 4 has been amended to recite "to said platelets" after "exogenous." Support for this amendment may be found on pages 9-10 of the specification. The basis of the present rejection of claim 4 is therefore believed to have been addressed and overcome.

(c) Claims 13 and 14. The Examiner alleges that the recitation of "an assay of said product" in claims 13-14 is indefinite since it is unclear what compounds and/or instruments are encompassed by "an assay" or the group of assays listed in claim 14. The rejection is

respectfully traversed. The specification at pp. 10-11 under the heading "Assays for Thrombin Generated from Modified Prothrombin" describes numerous assays for detecting the modified thrombin product of the invention, including those listed in claim 14. The methods are described and their detecting means are explained as they are commonly understood by those of ordinary skill in the art. Thus, the basis of the present rejection of claims 13-14 is not well taken. The rejection should be withdrawn.

For at least the reasons set forth above, claims 1-8 and 11-20 are not indefinite. Reconsideration of claims 1-8 and 11-20 and withdrawal of the rejection of these claims under 35 U.S.C. §112, second paragraph is requested.

(ii) Rejections Under 35 U.S.C. § 103(a).

Claims 1-4, 7-8, 11, 13-14, 16, and 19-20 have been rejected under as allegedly being obvious over Henriksen *et al.*, 66 *J. Clin. Invest.* 934 (1980) ("Henriksen"), in view of Hemker *et al.* U.S. Patent No. 5,266,462 ("Hemker").

The Examiner's position is that Henriksen describes a method for assaying prothrombin activation by providing a mixture of a prothrombin converting enzyme and a substrate and assaying a product that has the property that the product does not activate platelets, and that Hemker makes it obvious to add platelets to Henriksen's assay to arrive at the claimed invention. The rejection is traversed on the grounds that there is no motivation whatsoever in the prior art to combine Henriksen and Hemker.

Obviousness requires that each and every claim limitation be disclosed or suggested by the prior art. Henriksen and Hemker do not suggest the instant claims because they do not suggest assaying the activation state of platelets by reacting a mixture of platelets, a prothrombinase, and a substrate that is converted to a product that fails to activate platelets.

Henriksen fails because it does not suggest an assay of the activation state of platelets. To the extent that Henriksen discloses or suggests any assay, the Examiner correctly recognizes that it is "a method for assaying prothrombin activation" (*see* Office Action at page 3), i.e., a method for assaying the effect of converting wild-type prothrombin or mutant prothrombin Quick to thrombin or thrombin Quick, respectively. Such an assay does not assay the activation state of platelets. The assay disclosed in Henriksen and described by the Examiner

in the Office Action in the paragraph bridging pages 3-4 cannot "assay the activation the state of platelets" because there are no platelets present in the mixture.

The Examiner recognizes that Henriksen fails to suggest an assay that includes a mixture of platelets. The Examiner therefore attempts to cure Henriksen's defect with Hemker. The Examiner's attempt fails, however, because there is no suggestion in the prior art to combine these references. Both the motivation to combine the relevant elements and the suggestion of success must be found in the prior art to satisfy the requirements for maintaining an obviousness rejection. *In re The Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) ("[b]oth the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure"). The mere mention of elements in different references is not sufficient motivation to combine them to arrive at a claimed invention. *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998) ("[T]he examiner must show reasons that the skilled artisan, *confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.*") (citations omitted, emphasis added).

Hemker fails to include any suggestion to add platelets to Henriksen's assay to arrive at the claimed invention for an assay of platelet activation state. Hemker is concerned with determining the "excitability" of platelets. Hence, according to Hemker, "The amount of procoagulant phospholipids present at the outer membrane interface can be used to develop tests for determining the resting activity of platelets, the excitability of platelets, as well as the procoagulant activity of platelets in whole blood." Hemker, col. 3, lines 27-32. Hemker also states that, "the developed assay-system is a good tool to measure the susceptibility of platelets to thrombin induced activation." Hemker, col. 9, lines 4-6. One of ordinary skill in the art would understand that assays used to measure platelet "excitability" or the susceptibility of platelets to "thrombin induced activation" require production of a prothrombinase product that activates platelets, e.g., thrombin.

Hemker's express concern with the level of platelets activated by thrombin is diametrically opposed to the present claims' requirement that the product formed in claim 1 step (a) have the property that it not activate platelets. Accordingly, upon a fair reading of Hemker, taken as a whole, one of ordinary skill in the art would find no motivation to combine Hemker

with Henriksen to arrive at the instant claims because doing so would defeat Hemker's purpose of measuring platelet response to thrombin. It is an error to find obviousness where references "diverge from and teach away from the invention at hand." *W. L. Gore & Assoc. v. Garlock, Inc.*, 220 USPQ 303, 311 (Fed. Cir. 1983).

The Examiner, moreover, has tacitly acknowledged that Henriksen and Hemker are incompatible to arrive at the presently claimed invention.

As motivation for combining Henriksen and Hemker, the Examiner cites Hemker for the propositions that "assaying prothrombin activation in the presence of platelets 'is a good tool to measure the susceptibility of platelets to thrombin induced activation' ([Hemker,] col. 9, lines 4-6)" and that platelets are "useful in the development of drugs that inhibit platelet aggregation ([Hemker,] col. 15, lines 19-21)." The Examiner's reasoning is flawed, however, because these passages teach away from combining Henriksen and Hemker to arrive at the claimed invention, because they require combining platelets in a prothrombinase assay that leads to the formation of a product that activates platelets-- the first passage states expressly that the purpose of the assay is to measure susceptibility to thrombin induced activation and the second passage implicitly requires formation of a prothrombinase produce that activates platelets because the "development of drugs that inhibit platelet aggregation" implicitly requires that such drugs be present in a mixture of platelets and a platelet activating agent. (In the absence of a platelet activator, there would be no platelet aggregation to inhibit.)

Thus a fair reading of the passages in Hemker cited by the Examiner would at most suggest adding platelets to an assay that produces a product that activates platelets. Such an assays is diametrically opposed to the present claims' call for a substrate that cannot activate platelets. In short, instead of suggesting Applicants' invention, Hemker seeks to produce thrombin, a product that activates platelets, and is thus incompatible with the claimed invention. The Examiner's stated reason for combining Henriksen and Hemker must fail, accordingly.

Claims 5-6 and 15 have been rejected as allegedly being obvious over Henriksen and Hemker as applied to claims 1, 2, and 13, and further in view of Harris and Kozlowski, U.S. Patent No. 6,541,543 ("Harris"). Claims 12 and 17-18 have been rejected as allegedly being obvious over Henriksen and Hemker as applied to claims 1-3, 11, and 13, and further in view of Lottenberg *et al.*, 80 *Method Enzymol.* 341 (1981) ("Lottenberg").

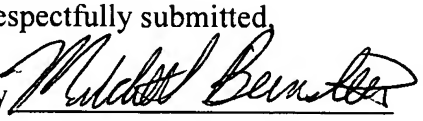
Harris is cited merely for the proposition that it teaches sulfo-N-succinimidyl acetate for derivatizing proteins. Lottenberg is cited merely for the proposition that it teaches the use of Tos-Gly-Pro-Arg-pNA chromogenic peptide for assaying thrombin activity. Nothing in Harris or Lottenberg cures Henriksen's defect of failing to suggest an assay mixture comprising platelets. Accordingly, the rejections that rely respectively on Harris or Lottenberg must fail for at least the reasons set forth above in the discussion of Henriksen and Hemker. The rejections should therefore be withdrawn.

For at least the reasons set forth above, claims 1-8 and 11-20 are not obvious over the prior art of record. Reconsideration of claims 1-8, and 11-20 and withdrawal of the rejections of these claims under 35 U.S.C.§ 103(a) is requested.

CONCLUSION

Claims 1-8 and 11-20 are believed to be in condition for allowance, which is earnestly solicited. If the Examiner believes that a telephone conference or a Supplementary Amendment would help advance the prosecution in the application, the Examiner is respectfully requested to call the undersigned attorney.

Respectfully submitted,

By 

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Mitchell Bernstein, Ph.D.
Registration No.: 46,550
Attorney for Applicant(s)

DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 753-6237 (fax)